

REMARKS

The presently claimed invention features methods for identifying compounds that are candidate modulators of the drug resistance of an eukaryotic cell. The presently claimed methods entail screening test compounds to identify those compounds that alter the expression of a gene encoding a polypeptide comprising the amino acid sequence encoded by SEQ ID NO:1, a gene whose expression is higher in an EMT-6 derived tumor selected for drug resistance than in an EMT-6 derived tumor that has not been selected for drug resistance.

Claims 23, 33 and 34 have been amended to recite "test compound" rather than simply "compound" in step (c). This amendment was made so that step (c) is consistent with step (a). Claims 39, 40, 47 and 48 have been cancelled. Claims 51-65 have been added. Support for these claims is found, for example, at pages 15, 16, 46 and 47 of the specification. No new matter has been added.

Rejection Under 35 U.S.C. §112, first paragraph (written description)

The Examiner rejected claims 23-27 and 29-50 under 35 U.S.C. §112, first paragraph as allegedly failing to be supported by an adequate written description.

The Examiner argued that the claims fail to meet the written description requirement because the specification does not describe the regulatory and non-coding regions of the gene corresponding to SEQ ID NO:1.

As a preliminary matter, Applicant emphasizes that Applicant is not claiming a gene. Applicant wishes to clarify this point because the Examiner twice implies that the Applicant is claiming a gene. For example, on page 2 of the Office Action the Examiner states that the "claims encompass the gene encoding the protein encoded by SEQ ID NO:1". On page 2 of the Office Action the Examiner also states that the "claims are drawn to a gene which encodes the protein encoded by SEQ ID NO:1". Both statements are incorrect. The claims are drawn to

Rather claiming a gene, the Applicant is claiming methods for screening test compounds to identify candidate modulators of drug resistance. To fulfill the written description requirement of 35 U.S.C. §112, first paragraph, the specification must "describe an invention and

do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention” *Regents of the University of California v. Eli Lilly & Co.*, 119 F.3d 1559 (Fed Cir. 1997). The present claims clearly meet this standard. The claims include a step of “determining the level of expression of a gene encoding a polypeptide comprising the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:1.” The reference to a “gene” in this step is simply a convenient manner for identifying the expression that is being measured. The actual measurement of expression depends on measurement of the mRNA produced by transcription of the gene or measurement of the polypeptide produced by translation of the transcribed mRNA. It cannot be disputed that the specification provides an adequate written description of both the mRNA and the polypeptide. A written description of the mRNA is provided by the disclosure SEQ ID NO:1, the cDNA sequence corresponding the mRNA sequence. A written description of the polypeptide is provided by translation of SEQ ID NO:1. Thus, the specification provides sufficient written description of the claimed invention—here a an assay method, not a gene--irrespective of the presence or absence of a written description of the gene.

In view of the forgoing, Applicant respectfully requests that this rejection be withdrawn.

Rejections Under 35 U.S.C. §112, first paragraph (enablement)

The Examiner rejected claims 23-27 and 29-50 under 35 U.S.C. §112, first paragraph, as allegedly not enabled. The Examiner argued that the present screening method claims are enabled only if the specification both: 1) enables the actual screening method for identifying compounds that are candidate therapeutic agents and 2) enables the use of the identified candidate compounds as therapeutic agents or in therapeutic methods. According to the Examiner, without the requirement the specification enable the use of the candidate compounds in therapeutic methods, the present claims would lack a specific and substantial utility.

The Examiners position regarding the required enablement is not warranted

Applicants disagree with the Examiner's position. The enablement requirement requires that claimed invention be enabled. Here the claimed invention is a screening method, not a

therapeutic compound or a therapeutic method. Thus, it is the screening method itself – not the therapeutic use of candidate compounds – that must be enabled for the enablement requirement of 35 U.S.C. §112, first paragraph, to be met. The Examiner argues that more is required. According to the Examiner, the claims will lack utility, i.e., they will not meet the requirements of 35 U.S.C. §101, unless the specification enables the therapeutic use of the candidate compounds identified in the screening method. The Examiner's position is unjustified and illogical. Moreover, the Examiner's position amounts to a *per se* rule that a claim to a screening method for identifying candidate compounds for use as therapeutic agents is not patentable.

In the Examiner's view, a screening method for identifying candidate compounds for use as therapeutic agents is not enabled unless the therapeutic use of the candidate compounds identified by the screen is enabled. Of course, prior to carrying out the screening method one does not know the identity of the compounds that will meet the criteria of the screening method. Yet the Examiner would require that the therapeutic use of these as yet unknown candidate compounds be enabled for the screening method to be enabled. This is, of course, a logical impossibility. Thus, the requirement that the Examiner seeks impose amounts to a *per se* rule that screening claims are not patentable because they cannot be enabled. Yet, screening claims are commonly granted. For example, U.S. 6,444,419 includes the following claim:

1. A method for screening for potential cancer therapeutics which comprises:

(a) performing a protease assay in the presence of a mutated TMPRSS2 polypeptide and in the presence of a compound suspected of being a cancer therapeutic, wherein the mutated TMPRSS2 polypeptide comprises a mutation which results in a polypeptide with altered protease activity when compared to the protease activity of a wild-type TMPRSS2 polypeptide comprising an amino acid sequence set forth in SEQ ID NO:2;

(b) performing a protease assay in the presence of the mutated TMPRSS2 polypeptide and in the absence of said compound suspected of being a cancer therapeutic;

(c) performing a protease assay in the presence of a wildtype TMPRSS2 polypeptide and in the presence of a compound suspected of being a cancer therapeutic; and

(d) comparing the amount of proteolysis in each of steps (a), (b) and (c) wherein when the presence of said compound results in an amount of proteolysis in step.

As another example, U.S. 6,649,362 includes to following claim:

1. A screening method for identifying a therapeutic candidate for a coronary heart disease or an inflammatory condition that comprises:

i) bringing at least one agent into contact with at least one component of a sphingosine kinase signaling pathway, under conditions such that an effect on the activity of said component is detectable, and

(ii) detecting the presence or absence of said effect, whereby detecting said effect indicates said agent as a therapeutic candidate with respect to coronary heart disease or an inflammatory condition.

Beyond the illogic of requiring the specification enable the therapeutic use of unidentified compounds, the Examiner's position that screening claims lack a substantial and specific utility unless the therapeutic use of the candidate compounds is enabled is at odds with the utility requirement. Target-based screening is used every day by large pharmaceutical companies, small start-up companies, and government and academic researchers the world over. Those carrying out drug development are well aware of the difficulty of developing a safe and effective therapeutic agent. However, they continue to use screening methods for identifying candidate compounds because they believe that such screens are useful for identifying potential therapeutic agents. Clearly, such screening methods have a specific, substantial real world utility.

The Examiner also argued that the scope of the present claims is not commensurate with the scope of enablement because few candidate therapeutic agents identified in screens will prove to be useful therapeutic agents. However, since it is widely understood that few compounds identified using screening methods prove to be useful therapeutic agents, the Examiner's reasoning again amount to a *per se* rule that screening claims are not patentable.

The present method claims are enabled

Applicant has clearly enabled the presently claimed screening methods. Pages 39-44 of the specification provide an extensive discussion of various assays formats as well as molecules

that can be screened. For example, at pages 39-40 a variety of sources of test compounds are described.

The test compounds of the present invention can be obtained using any of the numerous approaches in combinatorial library methods known in the art, including: biological libraries; natural products libraries; spatially addressable parallel solid phase or solution phase libraries; synthetic library methods requiring deconvolution; the 'one-bead one-compound' library method; and synthetic library methods using affinity chromatography selection. The biological library approach is limited to peptide libraries, while the other approaches are applicable to peptide, non-peptide oligomer or small molecule libraries of compounds (Lam, (1997) *Anticancer Drug Des.* 12:145).

Examples of methods for the synthesis of molecular libraries can be found in the art, for example in: DeWitt et al. (1993) *Proc. Natl. Acad. Sci. U.S.A.* 90:6909; Erb et al. (1994) *Proc. Natl. Acad. Sci. USA* 91:11422; Zuckermann et al. (1994). *J. Med. Chem.* 37:2678; Cho et al. (1993) *Science* 261:1303; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2059; Carrell et al. (1994) *Angew. Chem. Int. Ed. Engl.* 33:2061; and Gallop et al. (1994) *J. Med. Chem.* 37:1233.

Libraries of compounds may be presented in solution (e.g., Houghten (1992) *Bio/Techniques* 13:412-421), or on beads (Lam (1991) *Nature* 354:82-84), chips (Fodor (1993) *Nature* 364:555-556), bacteria (U.S. Patent No. 5,223,409), spores (Patent Nos. 5,571,698; 5,403,484; and 5,223,409), plasmids (Cull et al. (1992) *Proc. Natl. Acad. Sci. USA* 89:1865-1869) or on phage (Scott and Smith (1990) *Science* 249:386-390; Devlin (1990) *Science* 249:404-406; Cwirla et al. (1990) *Proc. Natl. Acad. Sci.* 87:6378-6382; and Felici (1991) *J. Mol. Biol.* 222:301-310).

Pages 14-22 and 45-47 of the specification include a description of various types of nucleic acids molecules that can be used to detect and assay mRNA corresponding to SEQ ID NO:1. For example, at page 46 various length probes are described.

A preferred agent for detecting a resistance mRNA or genomic DNA encoding a resistance protein is a labeled nucleic acid probe capable of hybridizing to the resistance mRNA or genomic DNA. The nucleic acid probe can be, for example, a full-length resistance mRNA, such as the nucleic acid of SEQ ID NO: 1, SEQ ID NO:2, SEQ ID NO:3, SEQ ID NO:5, SEQ ID NO:6, or a nucleic acid sequence depicted in Genbank Accession no.: X85993, L26081, L24118, M92357, M25324, M25280, W13166, X81627, K03235, U54705, or U04313, or

a portion thereof, such as an oligonucleotide of at least 15, 30, 50, 100, 250 or 500 nucleotides in length and sufficient to specifically hybridize under stringent conditions to the resistance mRNA or genomic DNA.

Pages 22-31 of the specification include description of various type of antibodies that can be used to detect and assay polypeptides encoded by the mRNA corresponding to SEQ ID NO:1.

Thus, the specification provides the teaching required to allow one of ordinary skill in the art to determine whether a test compound alters the "the level of expression of a gene encoding a polypeptide comprising the amino acid sequence encoded by the nucleotide sequence of SEQ ID NO:1 in an eukaryotic cell" Nothing more is required to meet the enablement requirement of 35 U.S.C. §112, first paragraph.

The claims are enabled for the use of cell other than EMT cells and for the use of cells in which the gene is not endogenous

The Examiner argued that the claims are not enabled for screening using cells which have a non-endogenous gene corresponding to SEQ ID NO:1 because, according to the Examiner, the specification "has not disclosed the regulatory region which control the expression of SEQ ID NO:1. The Examiner also argued that the claims are not enabled for screening using cells that are not EMT-6 derived cells.

Applicant has enabled screening using cells in which the gene corresponding to SEQ ID NO:1 is not endogenous. Nucleic acid molecules based on SEQ ID NO:1 can be used to isolate the corresponding genomic DNA, and this genomic DNA can be introduced into a selected cell. The isolation of genomic DNA using the corresponding cDNA is routine. Moreover, the specification, e.g., at page 16, describes the use of nucleic acid probes and primers to isolate genomic DNA.

Applicant cannot understand the basis for the Examiner's assertion that the claims are not enabled for screening using cells that are not EMT-6 cells. EMT-6 cells are not the only cells that include a gene corresponding to SEQ ID NO:1. The Examiner has not cited any evidence that the gene is not present or expressed in cells other than EMT-6 cells. Using the techniques

and nucleic acid molecules described in the specification, those this skilled in the art can readily identify cells that contain and express the gene corresponding to SEQ ID NO:1.

The specification enables one of ordinary skill in the art to practice the presently claimed screening methods. Nothing more is required to meet the enablement requirement.

In view of the forgoing, Applicant requests that the rejections under 35 U.S.C. §112, first paragraph for lack of enablement.

Rejections Under 35 U.S.C. §112, second paragraph

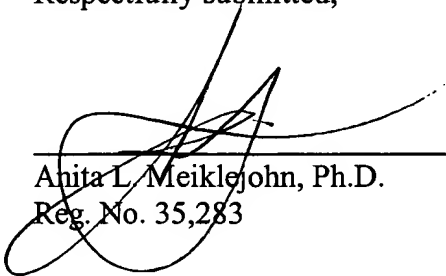
The Examiner rejected claims 39, 40, 47 and 48 under 35 U.S.C. §112, second paragraph. These claims have been cancelled, obviating this rejection.

CONCLUSION

Applicant believes that the claims are in condition for allowance. Please apply charges or credits to deposit account 06-1050.

Respectfully submitted,

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